REMARKS

Claims 27 and 38-85 were pending in the instant application. Claims 27, 60, 75-80, 84, and 85 have been amended. Support for the amendments to the claims can be found in the specification and claims, as originally filed. Upon entry of the present Amendment, claims 27 and 38-85 are pending and presented for reconsideration. Applicants respectfully submit that no new matter is introduced by the present Amendment.

In a Response to Restriction Requirement earlier filed on March 22, 2006, Applicants elected Group I, drawn to claims 27, 38-59, 79, and 81, without traverse. Applicants further elected the species of Type II diabetes, for search purposes only. It is the Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits is required, to which the claims will be restricted if no generic claim is finally held allowable. Applicants further understand that upon the allowance of a generic claim, they will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R.§1.141 *et seq.*

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action or any previous Office Action of the parent application, and was done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

No additional search is required and no new issues have been raised. Furthermore, in view of the arguments presented herein, the number of issues for appeal has been reduced. Therefore, Applicants respectfully request that the present Amendment be entered.

Acknowledgment of the Examiner's Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 52-55 under 35 U.S.C. 112, second paragraph, and the rejection of claims 38-42 and 45 under 35 U.S.C. 102(a) as being anticipated by Jiang *et al.*, as set forth in the Office Action dated June 12, 2006.

Rejection of claims 27, 38-59, 79, and 8-85 under 35 U.S.C. § 112, First Paragraph

Claims 27, 38-59, 79, and 81-85 have been rejected under 35 U.S.C. §112, first paragraph, because allegedly the specification, while being enabling for the methods *in vitro*, does not reasonably provide enablement for such methods performed *in vivo* . In particular, the Office Action states, on page 4, that "[t]his rejection could be overcome by requiring that the recited adipocytes must be 'isolated'."

Without acquiescing to this rejection and solely in an effort to further prosecution, Applicants have amended claims 27, 38-59, 79, and 81-85 to refer to "contacting an ***isolated*** adipocyte having a cell membrane." Applicants, therefore, respectfully request withdrawal of the rejection of claims 27, 38-59, 79, and 81-85 under 35 U.S.C. §112, first paragraph, and favorable reconsideration.

Claim Rejections - 35 U.S.C. §103

Rejection of claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259). The Examiner states on pages 4-5 of the Office Action that, "Al-Hasani taught methods of studying genes related to glucose transport. Specifically, Al-Hasani investigated the relationship between the GTPase dynamin and endocytosis of the GLUT4 glucose transporter in cultured rat adipocytes." The Examiner admits that, "Al-Hasani did not teach the use of siRNA." The Examiner then states that "Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the use of antisense or siRNA directed at the mRNA encoding the protein." In conclusion, the Office Action states, on page 5, that, "it would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA directed against dynamin to assess its role in the endocytosis of GLUT4."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence that one having ordinary skill in the art would have been motivated to combine

the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)).

I. The Cited References would not have Motivated nor would have Provided a Reasonable Expectation of Success to the Ordinary Skilled Artisan to Arrive at the Claimed Invention

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since the skilled artisan would have found neither the motivaton nor a reasonable expectation of success at arriving at the claimed invention given the teachings of the cited references.

The claims are directed to a method of identifying a gene that affects glucose transport, or a method of identifying a gene involved in an insulin response disease or disorder, the methods comprising: (a) contacting an isolated adipocyte having a cell membrane with an siRNA targeted against the gene, thereby forming a mixture; (b) electroporating the mixture under conditions such that the cell membrane becomes permeablized and the siRNA is introduced into the isolated adipocyte; (c) culturing the isolated adipocyte under conditions suitable for expression of the targeted gene and such that the siRNA mediates RNAi; and (d) assaying glucose transport in the isolated adipocyte, wherein a modulation in glucose transport indicates that the targeted gene affects glucose transport; thereby identifying a gene that affects glucose transport or a gene that is involved in an insulin response disease or disorder.

Al-Hasani *et al.* describe the characterization of the mechanism of GLUT4 endocytosis by overexpressing a dominant-negative mutant of dynamin-1 in rat adipose cells (see page 17504, column 2, lines 46-48 of Al-Hasani *et al.*). In order to study the role of dynamin in

GLUT4 endocytosis, Al-Hasani *et al.* overexpress a plasmid encoding a dominant-negative mutant of dynamin-1 in isolated rat adipose cells. The effects of dynamin-1 on GLUT4 trafficking are monitored using a co-transfected recombinant GLUT4 containing a hemaglutinin (HA) tag. The methodology of Al-Hasani is designed to transfect adipose cells with ***DNA and DNA expression plasmids*** (see, *e.g.*, page 17505, column 1, second paragraph of Al-Hasani *et al.*). In particular, the methods involve transfection of cells with large amounts of ***plasmid DNA*** (*e.g.*, 5 μg plasmid DNA per transfection). Large amounts of carrier DNA are utilized (*e.g.*, 100μg carrier DNA). Pulse conditions are specified for the described ***plasmid DNA*** transfection. The reference is silent as to capacitance.

Clancy *et al.* teach diagnostic assays for detecting bone and cartilage formation and threapeutic methods for treating disease and disorders related to bone and cartilage formation or respoption. Clancy *et al.* teach siRNAs as a component of a composition comprising "a plurality of antagonists of a plurality of genes" (see *e.g.*, para. [0009]). Clancy *et al.* also teach siRNAs as potential agents for "blocking or reducing the expression of a gene or the activity or level of the encoded polypetide that is modulated, *e.g.*, upregulated, during normal bone or cartilage formation" (see *e.g.*, para. 0239)).

Applicants respectfully submit that the ordinary artisan would not have been motivated to combine the teachings of the Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) with those of Clancy *et al.* (US 20030087259) to arrive at Applicants claimed methodology. Even if the skiled artisan were to rely on Clancy *et al.* for teaching that siRNAs as an agent capable of blocking gene expression, he would not have been motivated to substitute the ***DNA plasmids*** transfected in Al-Hasani with such siRNAs. The mere fact that Clancy *et al.* lists siRNAs and dominant negative mutants as potential gene blocking compounds in a more extensive list of gene blocking compounds, e.g., antisense molecules, ribozymes, triplexes, aptamers, does not arise to the level of a motivation to select one specific member from the recited antagonist list for use in the featured methodology. Moreover, there is nothing in Clancy et al. which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. In particular, Clancy relates to diagnostic and therapeutic methods for detecting and/or treating bone and cartilage formation and is wholey unrelated to the art of glucose transport.

The Office Action has failed to point to any teaching in the cited references which would impel one of ordinary skill in the art to combine the teachings of the references in order to arrive at the presently claimed invention. It is well-established law that the prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). Thus, absent evidence to the contrary, the combination of the two cited references amounts to an attempt at hindsight reconstruction of the claimed invention based on the teachings of Applicants' own specification and is clearly impermissible. See, for example, *In re Fine* 5 USPQ2d 1596 (Fed.Cir. 1988); *In re Gorman* 18 USPQ2d 1885 (Fed. Cir. 1991); *In re Fitch* 23 USPQ2d 1780 (Fed. Cir. 1990).

II. Lack of Reasonable Expectation of Success in Arriving at Applicants' Invention

Moreover, as indicated by the declaration of the inventors under 37 CFR §1.132, attached herein as Appendix A, prior to Applicants' demonstration that such electroporation of siRNA into adpocytes was possible according to the claimed methods of this invention, there was no reasonable expectation that such successful electroporation could be accomplished.

Even assuming arguendo that a skilled artisan might have been motivated to substitute siRNA for the plasmid DNA transfected in the Al-Hasani methodology, one would not have had a reasonable expectation that such a substitution would result in success. Specifically, it was well known in the art at the time of filing that electroporation of DNA into adipocytes only leads to the successful expression of DNA in only a small minority of the adipocytes (***approximately 1-10%***[1]). In contrast, in order for siRNA to successfully silence the gene of interest, *i.e.*, mediate RNA interference, as currently claimed, it is required that virtually all of the adipocytes (***approximately 100%***) take up functional siRNA. ***Since the successful electroporation of DNA into adipocytes is typically less than 10% efficient, it would <u>not</u> have been obvious to one of ordinary skill in the art at the time of filing of the instant invention that electroporation of siRNA into adipocytes would be nearly 100% efficient***[2]. A skilled artisan would have had an

[1] See, *e.g.*, page 40, lines 15-17 of the instant specification.
[2] Using labeled siRNA, Figure 1B, left panels, and Example 2, page 40, lines 1-17, of the specification demonstrate that the electroporation of siRNA into adipocytes was, unexpectedly, nearly 100% efficient.

appreciation of these significant differences and would not have reasonably expected that mere substitution of the siRNAs of Clancy *et al.* for the plasmid DNAs transfected in Al-Hasani *et al.* would be successful.

The art is also replete with teachings which support the non-obviousness of the present invention. Following are several examples demonstrating the difficulty of transfecting adipocytes with siRNA and the successful use of the present invention to electroporate adipocytes with siRNA:

(a) As demonstrated in Appendix B, in 2006 Robinson *et al.* state that "adipocytes are difficult to transfect, and until recently, successful siRNA transfection was achieved only via electroporation" (see, *e.g.*, page E885, second column, third full paragraph). Robinson *et al.* go on to cite a 2004 scientific publication of one of the inventors of the instant application, M. Czech, as the group which was successful in transfecting adipocytes with siRNA using electroporation.

(b) As demonstrated in Appendix C, the 2006 Panomics DeliverX Plus siRNA Transfection Kit Brochure discloses that "[t]ransfection of siRNA into differentiated 3T3-L1 adipocytes... has only been accomplished by electroporation" (see, *e.g.*, first page, left column) and specifically references the 2003 *Proceedings of the National Academy of Sciences* scientific publication by the instant inventors which corresponds to the instant patent application. This Brochure goes on to further disclose that "***adipocytes... represent one of the most difficult-to-transfect cell lines used routinely in cell biology studies***" (see, *e.g.*, page 2, right column, second full paragraph) (Emphasis added).

(c) As demonstrated in Appendix D, Jain discloses that "***adipocytes are fully differentiated cells with no proliferation and are thus difficult to transfect*** by either RNAi or ASO approaches" (see, *e.g.*, page 308, middle column, first paragraph) (Emphasis added).

(d) As demonstrated in Appendix E, Venugopal *et al.* disclose that "***adipocytes... proved difficult to transfect efficiently with siRNA***" (see, *e.g.*, page 17122, second column, first full paragraph) (Emphasis added).

Applicants also describe in their specificaition the problems existing in the art at the time of the invention. In particular, Applicants teach in the specification on page 1, lines 23-24 that adipocyte "cells are difficult to work with and are not easily transfected with reagents that work

in other cells such as fibroblasts." Furthermore, it was well known in the art at the time of the invention that the transfection of cells with DNA differs dramatically from the transfection of cells with siRNA, and that the transfection of siRNA varies greatly based on cell-type. For example, Walters and Jelinek[3] teach that the effectiveness of siRNAs may depend on the method of transfection (see title and abstract of Walters and Jelinek (2002) *Antisense and Nucleic Acid Drug Development* 12:411-418). More specifically, Walters and Jelinek teach the "striking dependence of dsRNA-mediated gene silencing in some cells on the methods of dsRNA transfection"(see Abstract of Walters and Jelinek). Additionally, Weil *et al.*[4] also teach that "the first difficulty with implementing RNA interference in a new cell type is optimizing the transfection procedure" (see page 1244, last paragraph of the Introduction, of Weil *et al.* (2002) *BioTechniques* 33:1244-1248).

These references indicate that, not only is the transfection of cells with siRNA different than transfection of cells with DNA, but siRNA transfection is complicated and the transfection procedure varies significantly from cell-type to cell-type. In summary, Applicants respectfully submit that the ordinarily skilled artisan at the time of Applicants' invention would not have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259).

In summary, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259). For the foregoing reasons, rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be reconsidered and withdrawn.

[3] A copy of which is attached herein as Appendix F.
[4] A copy of which is attached herein as Appendix G.

Rejection of claims 38-43, 84, and 85 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 38-43, 84, and 85 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Paquerequ *et al.* (Anal. Biochem. 204(1):147-151, 1992). The Examiner's comments with respect to Al-Hasani and Clancy are summarized above. The Office Action states that "Paquereau taught a method of delivering nucleic acids to mammalian cells by electroporation using a potential of 0.15-0.2kV and a capacitance of 960 micro F." In summary, the Office Action states that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the electrical potential and capacitance used in the electroporation of the cells of Al-Hasani because it was recognized in the art that these variables could affect the amount of cell damage caused by electroporation, as well as cellular survival after electroporation."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The currently pending claims are directed to a method of identifying a gene in an adipocyte that affects glucose transport or a gene involved in an insulin response disease or disorder.

The legal requirements to establish a *prima facie* case of obviousness are set forth above. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since at the time the invention was made there was no motivation to combine the references in the manner suggested by the Examiner, nor was there a reasonable expectation of success in making the claimed invention. The teachings of Al-Hasani *et al.* and Clancy *et al.* are set forth above. As discussed previously, the Examiner has not provided the requisite motivation to combine these references. In addition, based on the teachings of the references, there was no reasonable expectation of success in making the claimed invention based on the teachings of these references.

The Paquereau reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Paquereau describes the transfection of ***hepatocyte cells with DNA*** (see e.g., page 148, column 2, lines 1-4 of Paquereau *et al.*). In particular, Paquereau describes the electroporation of high concentrations of isolated hepatocytes (*e.g.*, 16-20 x 10^6 heaptocites, *i.e.*, 20-25 x 10^6 hepatocytes per 0.8 ml) with large amounts of

plasmid DNA (*e.g.*, 30 μg DNA per 0.8ml) in the presence of large amounts of carrier DNA (*e.g.*, 400 um). The transfection methods are optimized to obtain high levels of expression of the reporter gene CAT. As discussed previously, siRNAs and plasmid DNA are quite different chemical entities. Accordingly, one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in utilizing certain of the parameters disclosed in Paquereau for transfection of large amounts of plasmid DNA to arrive at the siRNA electroporation methods featured in the claimed invention based upon this teaching, nor would one be motivated to combine these references. Moreover, there is nothing in Paquereau *et al.* which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* and Clancy *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. Paquereau *et al.* relates to DNA transfection of hepatocytes to preserve a growth hormone response and is wholey unrelated to the art of glucose transport.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Paquerequ *et al.* (Anal. Biochem. 204(1):147-151, 1992). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claims 38-43, 84, and 85 under 35 U.S.C. §103(a) and favorable reconsideration.

Rejection of claim 49 under 35 U.S.C. § 103(a)

The Examiner has rejected claim 49 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). The Examiner's comments with respect to Al-Hasani and Clancy are summarized above. The Examiner states that, "Standaert taught methods of studying the effect of a gene expression of protein kinase C zeta (PKC-zeta) on glucose transport." The Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Al-Hasani to studies of glucose uptake."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The currently pending claims are directed to a method of identifying a gene that affects glucose transport or a gene involved in an insulin response disease or disorder.

The legal requirements to establish a *prima facie* case of obviousness are set forth above. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since at the time the invention was made there was no motivation to combine the references in the manner suggested by the Examiner, nor was there a reasonable expectation of success in making the claimed invention. The teachings of Al-Hasani *et al.* and Clancy *et al.* are set forth above. As discussed previously, the Examiner has not provided the requisite motivation to combine these references. In addition, based on the teachings of the references, there was no reasonable expectation of success in making the claimed invention based on the teachings of these references.

The Standaert reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Standaert, like Al-Hasani, is directed toward the study of insulin stimulation in glucose transport by transfection of ***rat adipocytes with plasmid DNA*** (see *e.g.*, page 148, column 2, lines 1-4 of Standaert *et al.*). Like Al-Hasani, Standaert fails to rectify the deficiency of teaching of features necessary to electroporation of siRNAs as in the claimed invention. Applicants submit that one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in making the claimed invention based upon this teaching, nor would one be motivated to combine these references.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claim 49 under 35 U.S.C. §103(a) and favorable reconsideration.

Rejection of claims 52-55 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 52-55 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of McSwiggen *et al.* (US Patent 7,022,828). The Examiner states on page 10 of the Office Action that, "[t]he teachings of Al-Hasani and Clancy... can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation." Further, on page 11, the Office Action states that "McSwiggen taught methods of inhibiting gene expression using siRNA, and taught that the stability of siRNA molecules could be enhanced through the use of modified bases." In conclusion, the Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to use modified siRNA oligonucleotides in the invention of Al-Hasani as modified by Clancy... in order to enhance the function of the oligonucleotides, as taught by McSwiggen."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The McSwiggen reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. McSwiggen teaches modified siRNA oligonucleotides which modulate the expression or function of IKK genes, such as IKK-gamma, IKK-alpha, or IKK-beta, and PKR genes in several cell types. However, McSwiggen does disclose any details of transfecting ***adipocytes*** with siRNA. Thus, McSwiggen fails to rectify the deficiency of teaching of the Al-Hasani and Clancy references. Moreover, there is nothing in McSwiggen which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* and Clancy *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. McSwiggen relates generically to the chemistry of siRNA derivatives and is wholey unrelated to the art of glucose transport.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.*

(US 20030087259) and further in view of McSwiggen *et al.* (US Patent 7,022,828). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claims 52-55 under 35 U.S.C. §103(a) and favorable reconsideration.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks presented, favorable reconsideration and withdrawal of the rejections, and allowance of this application with the pending claims are respectfully requested. If a telephone conversation with the Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: July 25, 2007

Respectfully submitted,

By _____

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